



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,497	02/24/2004	Mark W. Becker	249.P2	9922
25000 7590 12/19/2006 GILEAD SCIENCES INC 333 LAKESIDE DR FOSTER CITY, CA 94404			EXAMINER MARTIN, PAUL C	
			ART UNIT	PAPER NUMBER
			1657	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		12/19/2006	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

**Office Action Summary**

Application No.

10/785,497

Applicant(s)

BECKER ET AL.

Examiner

Paul C. Martin

Art Unit

1657

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 14 September 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3-13 and 15-17 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-13 and 15-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

Claims 1, 3-13 and 15-17 are pending in this application and were examined on their merits.

### ***Information Disclosure Statement***

The information disclosure statement filed 07/19/04 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Copies of the foreign patents and all of the cited non-patent literature have not been received and scanned as of the filing of the latest IDS, which was filed 07/19/04.

### ***Specification***

The use of the trademarks Chiralpak and Zorbax has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Art Unit: 1657

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

### ***Claim Objections***

The objections to Claims 4, 5 and 12 has been withdrawn due to the Applicant's amendment to the Claims filed 09/14/06.

### ***Claim Rejections - 35 USC § 112***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of Claim 7 under 35 USC § 112, 2<sup>nd</sup> paragraph as being indefinite for lacking sufficient antecedent basis for the term "amidate" has been withdrawn due to the Applicant's amendment to the Claim filed 09/14/06.

### ***Claim Rejections - 35 USC § 102***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Art Unit: 1657

The rejection of Claims 1, 3-5, 9 and 14-16 under 35 USC § 102 (b) as being anticipated by Glazier *et al.* (US 5,627,165) has been withdrawn due to the Applicant's amendment to the Claims filed 09/14/06.

Claims 1 and 3-7 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Shaw *et al.* (1997). This is a new rejection necessitated by the Applicant's amendment to the Claims file 09/14/06.

Shaw *et al.* teaches a screening method comprising the steps of; providing an amino acid phosphonoester prodrugs of PMPA (Pg. 1825, Table 1), selecting a target tissue (plasma) and non-target tissues (liver and intestine), administering the prodrug to both tissues and determining the relative *in vitro* biological stability and bioavailability of PMPA in the tissues (Pg. 1827, Column 1, Lines 7-8 and Column 2, Lines 1-14 and Table 3, and Pg. 1828, Column 1, Lines 1-10).

Shaw *et al.* teaches wherein the prodrug of PMEA was shown to significantly increase the oral bioavailability of PMEA in HIV infected patients and wherein PMPA has selective and potent inhibitory activity *in vitro* against retroviruses and wherein IV PMPA has been shown to reduce viral load in HIV infected patients (Pg. 1824, Column 2, Lines 1-9 and 16-18).

Shaw *et al.* teaches the administration of the PMPA prodrug to live dogs and the determination of the relative activity by analysis of the animal tissue after administration of the prodrug, wherein the activity is determined the amount of PMPA in the tissue (Pg. 1827, Fig. 2).

It is inherent in the method of Shaw *et al.* that the screening method would determine the relative antiviral activity conferred by the PMPA prodrug in the target and non-target tissues because PMPA is a known potent antiviral compound and the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues would necessarily also provide a determination of the *relative* antiviral activity of the prodrug in those tissues even if no virus were present in the tissues.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-7 and 10-13 rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw *et al.* (1997). This is a new rejection necessitated by the Applicant's amendment to the Claims file 09/14/06.

The teachings of Shaw *et al.* were discussed above.

Shaw *et al.* does not teach a method wherein the target and non-target tissues are in an animal, and the pro-drug is administered to the animal and the relative activity is determined by assaying the amount of at least one metabolite of the prodrug in the tissues after administration of the prodrug, wherein the metabolite is the parental drug or a diphosphate of the parental drug. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the screening method to determine the bioavailability and biostability of PMPA prodrugs as taught by Shaw *et al.* above by administering the prodrugs to a live animal and determining the relative activity of the prodrugs in both target and non-target tissues by assaying the amount of the parental drug in the tissues after administration of the prodrug because one of skill in the art would have recognized that the tissue culture biostability method and blood bioavailability method of Shaw *et al.* could be combined with little change to the methods as all of the essential elements were present to make this modification. One of ordinary skill in the art would have recognized that the metabolite could appear in alternate forms depending upon the prodrug administered and that the diphosphate form of PMPA would have been an obvious variation on the parental drug, PMPA.

Art Unit: 1657

One of skill in the art would have been motivated to make this modification in order to assess the bioavailability and biostability of the prodrugs in a living system beyond the tissue culture homogenates to assess the affects of other variables (enzymes, hormones, etc.) on the prodrugs that may not be present in tissue homogenates. There would have been a reasonable expectation of success in making this modification because Shaw *et al.* already teaches the administration and determination of PMPA from PMPA prodrugs in three types of tissues and the administration and determination of PMPA from PMPA prodrugs in blood from live dogs following administration of the prodrugs.

Claims 1, 3-7, 9-13, 15 and 16 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw *et al.* (1997) in view of Glazier *et al.* (US 5,627,165).

The teachings of Shaw *et al.* were discussed above.

Shaw *et al.* does not teach selecting a prodrug having a relative activity in the target tissue that is greater than 10 times that of the non-target tissue, wherein the target tissue is lymphoid tissue and the activity is anti-HIV activity, wherein the target tissue is liver tissue and the activity is anti-HBV or wherein the target tissue is hematological and the activity is antitumor activity.

Glazier *et al.* teaches a method of screening for antiviral activity of PMEA [9-(2-phosphonylmethoxyethyl)adenine] prodrugs on HIV infected human T-lymphocyte (lymphatic tissue) (CEMss) and HBV infected hepatocytes (liver tissue) and by administering the prodrug to a target tissue (HIV/HBV infected) and a non-target (uninfected) control; and determining the antiviral activity conferred by the prodrug on the tissues and selecting a prodrug having an activity in the infected tissue greater than 10 times that of the non-infected tissue. (Column 36, Lines 35-48 and Column 37, Lines 5-22 and Columns 38 and 39, Tables).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the screening method to determine the bioavailability and biostability of PMPA prodrugs as taught by Shaw *et al.* above with the method of screening for antiviral activity of phosphonoamidate prodrugs of Glazier *et al.* because one of ordinary skill in the art would have recognized that both methods are drawn to the determination of the relative antiviral activities of phosphonoamidate prodrugs in various tissue types. One of ordinary skill in the art would have been motivated to make this combination because of the advantage demonstrated by Glazier *et al.* of being able to directly determine the specific antiviral activity of the prodrugs against specific viruses in specific target tissues, such specificity not being determined in the method of Shaw *et al.* which only determined the relative general antiviral activity in target tissues.

Art Unit: 1657

There would have been a reasonable expectation of success in making this combination because both methods are drawn to the characterization of the levels of antiviral activity seen during the administration of phosphonoamidate prodrugs to animal tissues.

Claims 1, 3-8, 10-13 and 17 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw *et al.* (1997) in view of Starrett *et al.* (US 5, 663, 159).

The teachings of Shaw *et al.* were discussed above.

Shaw *et al.* does not teach wherein the phosphonoester is an aryl ester, or wherein the target tissue is hematological and the activity is antitumor activity.

Starrett *et al.* teaches the administration of an aryl ester phosphonoester PMEA prodrug to rats and assaying the amount of metabolite of the parental prodrug PMEA that is bioavailable based on urine excretion data (Column 9, Lines 59-67 and Column 10, Tables).

Starrett *et al.* teaches wherein PMEA was found to have anti-tumor activity against intraperitoneal P388 leukemia (Column 2, Lines 40-41).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the screening method to determine the bioavailability and biostability of PMPA prodrugs as taught by Shaw *et al.* above with the method of Starrett *et al.* for determining the metabolism of an aryl ester prodrug with anti-tumor activity in rats because both methods are directed to the bioavailability of phosphoramidate prodrugs in animals. One of ordinary skill in the art would have been motivated to make this combination because Shaw *et al.* already teaches wherein the target tissue was hematological and the activity was antiviral and combination of the method of Starrett *et al.* which teaches the use of the aryl ester prodrug of PMEA would confer provide an assessment of the relative antitumor activity in both the target tissue (blood) and non-target tissues (liver and intestine). There would have been a reasonable expectation of success in combining these two methods because both are drawn to the characterization of the metabolism and bioavailability of prodrugs in animals.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusion***

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

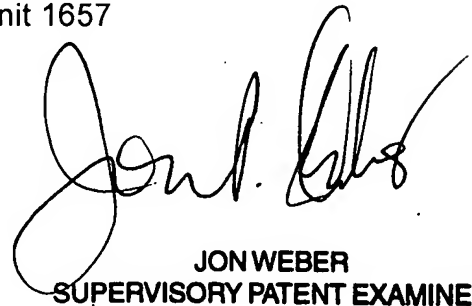
Art Unit: 1657

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin  
Examiner  
Art Unit 1657

12/06/06



**JON WEBER**  
**SUPERVISORY PATENT EXAMINER**